

Package leaflet: Information for the user
ESTRING® 7.5 microgram/24 hours, vaginal delivery system
Estradiol Hemihydrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any of the side effects gets serious, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What ESTRING is and what it is used for
2. What you need to know before you use ESTRING
3. How to use ESTRING
4. Possible side effects
5. How to store ESTRING
6. Contents of the pack and other information

1. What ESTRING is and what it is used for

ESTRING vaginal delivery system is a vaginal ring which contains the active ingredient estradiol hemihydrate, which is a naturally occurring form of the main female sex hormone, oestrogen.

Women's ovaries gradually produce less oestrogen as they approach menopausal age (also referred to as "the change"). Low levels of oestrogen can cause symptoms such as vaginal dryness, inflammation or itching, and this in turn can lead to sore or painful sexual intercourse, and an increased susceptibility to vaginal or urinary infections.

ESTRING vaginal delivery system is part of hormone replacement therapy (HRT) that acts locally in the vagina to maintain the adequate levels of oestrogen to relieve these symptoms in post menopausal women. It does not treat other symptoms of menopause such as hot flushes and sweats. Tell your doctor if you also have these problems.

2. What you need to know before you use ESTRING

Medical check-up

ESTRING may not be suitable for all women. Before you start using ESTRING, your doctor should ask about your own and your family's medical history. Your doctor may decide to examine your breasts and/or your abdomen, and may do an internal examination - but only if these examinations are necessary for you, or if you have any special concerns.

Once you've started on HRT, it is recommended that you see your doctor for regular check-ups (at least once a year). At these check-ups, your doctor may discuss with you the benefits and risks of continuing to use HRT.

Be sure to:

- **go for regular breast screening and cervical smear tests**

- **regularly check your breasts** for any changes such as dimpling of the skin, changes in the nipple, or any lumps you can see or feel

Do not use ESTRING if you have the following conditions:

- you are allergic to estradiol or similar medicines for hormone replacement therapy, or any of the other ingredients of this medicine (listed in section 6)
- hereditary blood disorder (porphyria)
- cancer that is sensitive to oestrogen e.g. endometrial cancer (cancer of the womb) or if you are suspected of having it
- previous or current history of an ‘embolus’ (blood clots that travel through the bloodstream and block blood vessels in the leg or elsewhere, also called ‘deep vein thrombosis’ (DVT))
- you have or have ever had breast cancer, or if you are suspected of having it
- vaginal bleeding which you have not made your doctor aware of
- previous or current liver disease where liver function tests are still abnormal
- overgrown lining of your womb (untreated endometrial hyperplasia)
- previous or a present case of blocked arteries that could cause cardiovascular diseases like angina or a heart attack
- blood clotting disorder (thrombophilic disorder such as protein C, protein S or antithrombin deficiency).

If any of the above conditions appear for the first time while using ESTRING, stop using it at once (remove the ring if possible) and consult your doctor immediately.

Warnings and precautions

Talk to your doctor or pharmacist before using ESTRING

Your doctor will assess your health and discuss the risk and benefits of hormone replacement therapy carefully before prescribing ESTRING to you. Tell your doctor if you currently have or have had in the past any of the following conditions to help them decide if you will be suitable for treatment with ESTRING:

- A prolapse (weakening of the structures supporting your internal organs) or have ever had an operation for prolapse
- You are on long term steroid therapy or have problems with your adrenal glands such as a disease called Cushing’s disease (where you may experience thinning or reddening of the skin)
- Vaginal discomfort, bleeding or pain in your vagina including irritation or discharge which may be due to ulcers or infection
- If you have a short narrow vagina from previous surgery or the effect of a condition called vaginal atrophy
- Fluid retention due to cardiac or kidney problems
- High levels of triglycerides (a type of fat) in your blood
- Liver diseases (including liver tumours)
- Diabetes
- History of cancer (particularly breast cancer) in your family
- Risk factors for blood clots in the veins (venous thromboembolism or deep vein thrombosis), see later in section 2 where the risks of using ESTRING are described
- High blood pressure
- Migraine or severe headache
- Uterine fibroids (growth on the walls of the womb)
- Fits (epilepsy)
- Gallstones
- Autoimmune disease, systemic lupus erythematosus (SLE)

- History of endometrial hyperplasia (an increase in the number of cells of the inner lining of the womb)
- Endometriosis (inner lining tissues of the womb found in places other than the womb)
- Problems with your hearing caused by scarring in the ear (otosclerosis)
- Asthma
- Hereditary and acquired angioedema

If any of the above conditions get worse or come back while you are using ESTRING you should remove ESTRING vaginal delivery system and see your doctor straight away.

Stop using ESTRING (remove the ring if possible) and see a doctor immediately

If you notice any of the following when using HRT remove ESTRING vaginal delivery system and see your doctor straight away. If you experience difficulty or pain when trying to remove the vaginal ring please do not continue and see your doctor:

- if you develop any of the conditions mentioned in the ‘DO NOT use ESTRING’ section;
- if you develop yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease;
- if you develop a swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing which are suggestive of an angioedema;
- if you experience a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness);
- if you get migraine-like headaches which happen for the first time;
- if you become pregnant;
- if you notice signs of a blood clot, such as:
 - painful swelling and redness of the legs;
 - sudden chest pain;
 - difficulty in breathing;
 For more information, see ‘Blood clots in a vein (thrombosis)’

Note: ESTRING is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking oestrogen-only HRT tablets for a long time can increase the risk of developing cancer of the womb lining (the endometrium).

It is uncertain whether there is a similar risk with ESTRING which is used for repeated or long term (more than one year) treatments. However, ESTRING has been shown to have very low absorption into the blood, therefore the addition of a progestagen is not necessary.

If you get bleeding or spotting, it’s usually nothing to worry about, but you should promptly make an appointment to see your doctor. It could be a sign that your endometrium has become thicker.

The following risks apply to HRT medicines which circulate in the blood. However ESTRING is for local treatment in the vagina and the absorption into the blood is very low. It

is less likely that the conditions mentioned below will get worse or come back during treatment with ESTRING, but you should see your doctor if you are concerned.

Breast cancer

Evidence suggests that using ESTRING does not increase the risk of breast cancer in women who had no breast cancer in the past. It is not known if ESTRING can be safely used in women who had breast cancer in the past.

- **Regularly check your breasts. See your doctor if you notice any changes such as:**
 - dimpling of the skin;
 - changes in the nipple;
 - any lumps you can see or feel;

Additionally, you are advised to join mammography screening programs when offered to you.

Ovarian cancer

Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users (i.e. about 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (thrombosis)

The risk of **blood clots in the veins** is about 1.3 to 3- times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, **and if one travels to the lungs**, it can cause chest pain, breathlessness, fainting or even death. This condition is called **pulmonary embolism**, or **PE**.

DVT and PE are examples of a condition called **venous thromboembolism**, or **VTE**.

You are more likely to get a blood clot in your vein as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:

- if you have cancer
- if you are seriously overweight
- if you have had a blood clot before
- if any of your close family have had blood clots
- if you have had one or more miscarriages
- if you have any blood clotting problem that needs treatment with a medicine such as warfarin
- if you're off your feet for a long time because of major surgery, injury or illness
- if you have a rare condition called SLE.

If any of these things apply to you, talk to your doctor to see if you should use HRT.

Looking at **women in their 50s** who are **not taking HRT** - on average, over a 5-year period, 4-7 in 1000 would be expected to get a blood clot in a vein.

For **women in their 50s** who have been **taking** oestrogen-only **HRT**, for over 5 years, there will be 5 to 8 cases in 1000 users (i.e. 1 extra case).

If you get:

- painful swelling in your leg
- sudden chest pain
- difficulty breathing

See a doctor as soon as possible and **do not use any more HRT** until your doctor says you can. These may be signs of a blood clot.

If you're going to have surgery, make sure your doctor knows about it. You may need to stop using HRT about 4 to 6 weeks before the operation, to reduce the risk of a blood clot. Your doctor will tell you when you can start using HRT again.

Heart disease

For women taking oestrogen-only therapy there is no increased risk of developing a heart disease.

Stroke

The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age. Other things that can increase the risk of stroke include:

- getting older
- high blood pressure
- smoking
- drinking too much alcohol
- an irregular heartbeat

If you are worried about any of these things, or if you have had a stroke in the past, talk to your doctor to see if you should use HRT.

Looking at **women in their 50s** who are **not taking HRT** - on average, over a 5-year period, **8 in 1000** would be expected to have a stroke.

For **women in their 50s** who are **taking HRT**, the figure would be **11 in 1000**, over a 5-year period (i.e. an extra 3 cases).

If you get:

- unexplained migraine-type headaches, with or without disturbed vision

See a doctor as soon as possible and **do not use any more HRT** until your doctor says you can. These headaches may be an early warning sign of a stroke.

Other information

HRT will not prevent memory loss. In one study of women who started using combined or oestrogen-only HRT after the age of 65, a small increase in the risk of dementia was observed.

Women with hypertriglyceridaemia may experience large increases of their plasma triglycerides, which can lead to inflammation of the pancreas (pancreatitis). Symptoms of pancreatitis may include abdominal pain, abdominal swelling, fever and feeling or being sick.

Blood tests

If you are about to have any blood tests, (e.g. to test for presence of an excess of triglycerides (a type of fat found in the blood)), you must tell your doctor that you are using ESTRING vaginal delivery system, as these tests can be affected by use of the vaginal delivery system.

Other medicines and ESTRING

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular, tell your doctor if you are taking:

- Anticonvulsants used in the treatment of epilepsy such as phenobarbitol, phenytoin, or carbamazepine
- Anti-infectives such as rifampicin, rifabutin
- Drugs used to treat HIV such as ritonavir, nelfinavir, nevirapine, or efavirenz
- Herbal preparations containing St. John's wort (*Hypericum perforatum*).

It is recommended that the ring is removed when constipated or using vaginal preparations.

Pregnancy and breast-feeding

ESTRING should not be used during pregnancy. If you become pregnant whilst using ESTRING, you should stop using ESTRING immediately (remove the ring if possible) and tell your doctor that you are pregnant. ESTRING should not be used whilst breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine while breast-feeding.

Driving and using machines

There are no special precautions, you can drive or operate machinery as long as you feel well.

3. How to use ESTRING

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Please follow the instructions below carefully. You should wash your hands thoroughly before inserting ESTRING vaginal delivery system.

To insert ESTRING vaginal delivery system into your vagina

- Relax and find a position which feels comfortable for you.
- Either stand with one foot on a chair or lie on your back with your knees bent up.
- With one hand, open the folds of skin around the vagina.
- With the other hand, press the ring into an oval.
- Push the ring into your vagina as far as it will go - upwards and backwards towards the small of the back.
- Finally, wash your hands.

If the ring falls out, it should be rinsed in lukewarm (not hot) water and then reinserted.

While using ESTRING vaginal delivery system

You may be aware of the ring at first but this feeling should go away. The ring may take several weeks to have the full effect. As the ring begins to work you may notice an increase in vaginal lubrication (wetness), this is normal and should be the same as you experienced before the menopause.

Most women and their partners have found it acceptable for the ring to stay in place during sexual intercourse. If you or your partner finds the ring uncomfortable or unacceptable it may be removed. The ring may move down in the vagina and become noticeable during straining to empty your bowels. If this happens the ring can be easily pushed back into position with your finger.

If you know that you are constipated or need to strain to empty your bowels then you should remove the ring first.

To take out ESTRING vaginal delivery system from your vagina

- Relax and find a position which feels comfortable for you.
- Either stand with one foot on a chair or lie on your back with your knees bent up.
- With one hand, open the folds of skin around the vagina.
- With the other hand, hook your finger around the ring.
- Pull the ring gently downwards and forward.
- Finally, wash your hands.

How long you should use your ring for

Each ring should be worn continuously for 3 months, and then replaced by a new ring, as appropriate. The maximum recommended duration of continuous therapy is two years. Your doctor will try to give you the lowest effective dose possible, and HRT should only be continued as long as the benefit in relief of severe symptoms outweighs the risk.

Routine examinations whilst using ESTRING vaginal delivery system

It is recommended that you have regular screening through the National Breast Cancer Screening Programme and National Cervical Cancer Screening Programme. Your doctor can provide details. You are also recommended to report any changes in your breasts to your doctor as soon as possible.

If you stop using your ring

Your symptoms may return after about 3 weeks.

Use in children

ESTRING vaginal delivery system is not recommended for use in children.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following diseases are reported more often in women using HRT medicines which circulate in the blood compared to women not using HRT. These risks apply less to vaginally administered treatments such as ESTRING:

- ovarian cancer;
- blood clots in the veins of the legs or lungs (venous thromboembolism);
- stroke;
- probable memory loss if HRT is started over the age of 65;

For more information about these side effects, see section 2.

If you develop any of the conditions listed under ‘Do not use ESTRING’ if you have the following conditions’ or those listed under “ Stop using ESTRING (remove the ring if possible) and see a doctor immediately” or if you have any of the following side-effects, remove ESTRING vaginal delivery system and see your doctor straight away. If you experience difficulty or pain when trying to remove the vaginal ring please do not continue and see your doctor.

- symptoms of an allergic reaction. This may include skin rash, hives, itching. This occurs **uncommonly** (may affect up to 1 in 100 people using **ESTRING**)
- persistent or severe vaginal discomfort, ulceration or swelling after the ring has been inserted.
This occurs **rarely** (may affect up to 1 in 1000 people using **ESTRING**)

There have been rare reports of the vaginal ring becoming attached to the vaginal wall, making ring removal difficult. Some women have needed surgery to remove the vaginal ring.

Common side effects may affect up to 1 in 10 people using the **ESTRING** vaginal delivery system:

- Urinary tract infection
- Infection and itching inside and around the vagina
- Discomfort/pain in the stomach area (abdomen)
- Any persistent feeling of the ring in the vagina or pressing on the bladder/rectum (back passage)
- Pain on passing urine
- Generalised itching
- Increased sweating

The symptoms mentioned above occur more frequently in untreated post-menopausal women.

Other side effects reported during treatment of patients with other forms of oestrogen therapy include:

Common side effects may affect up to 1 in 10 people

- depression
- hair loss
- joint pain
- leg cramps
- unusual or unexpected breakthrough bleeding or spotting
- vaginal discharge
- breast pain, breast tenderness, swollen breasts, discharge from the nipples
- changes in weight (increase or decrease)
- changes in your triglyceride levels (fatty substances in the blood)

Uncommon side effects may affect up to 1 in 100 people

- blood clot in the leg or lungs See “**Stop using ESTRING and see a doctor immediately**”
- vaginal inflammation
- vaginal thrush
- changes in your interest in sex (increased or decreased libido)
- changes in your mood
- anxiety
- headache or migraine
- dizziness

- difficulty wearing contact lenses
- feeling sick, a feeling of being bloated, abdominal pain
- gallbladder disease
- discoloration of the skin especially of the face or neck known as “pregnancy patches” (chloasma);
- increase in hair growth
- itchy skin
- rash
- changes in menstrual flow
- changes in vaginal discharge
- visible swelling of the face or ankles

The following side effects have been reported with other HRTs:

Not known (frequency cannot be estimated from the available data)

- memory loss (dementia)
- painful reddish skin nodules (erythema nodosum)
- rash with target-shaped reddening or sores (erythema multiforme)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ESTRING

Do not store above 25°C.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and also on the foil pouch after EXP. The expiry date refers to the last day of that month.

Do not use ESTRING vaginal delivery system if it is discoloured, misshapen, or does not have a smooth surface.

Used rings still contain some of the active hormonal ingredient. The used ring should be placed within the original pouch or in a plastic bag, then sealed and discarded safely, out of the reach and sight of children.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ESTRING contains

The active substance in ESTRING is estradiol hemihydrate 2 mg, corresponding to 1.94 mg estradiol.

The other ingredients are silicone fluid, barium sulfate, silicone elastomer Q7-4735A, silicone elastomer Q7-4735B.

What ESTRING looks like and contents of the pack

ESTRING vaginal ring is a slightly opaque ring made of a silicone elastomer, with a whitish core, containing a drug reservoir of the active ingredient, estradiol hemihydrate.

ESTRING is individually packed in a heat-sealed rectangular pouch consisting of, from outside to inside: Polyester/Aluminium foil/Low density Polyethylene. Each pouch is provided with a tear-off notch on one side and is packed into a cardboard carton.

Marketing Authorisation Holder and Manufacturer

The manufacturing authorisation holder is Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK.

The manufacturer is Sever Pharma Solutions AB, Agneslundsvägen 27, 212 15, Malmö, Sweden

Company Contact address

For further information on this medicine, please contact Medical Information at Pfizer Limited in Walton Oaks, Tadworth, Surrey.

Tel: +44 1304 616161.

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Spain, France, Italy, Slovenia, United Kingdom (Northern Ireland)	Estring
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